Statistical Analysis Plan H6D-MC-LVIG (b)

A Multiple Ascending Dose Study of Tadalafil to Assess the Pharmacokinetics and Safety in a Pediatric Population with Pulmonary Arterial Hypertension

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1. Title Page

Statistical Analysis Plan for Protocol H6D-MC-LVIG:
A Multiple Ascending Dose Study of Tadalafil to Assess the Pharmacokinetics and Safety in a Pediatric Population with Pulmonary Arterial Hypertension

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Tadalafil (LY450190)

Study H6D-MC-LVIG is a Phase 1b/2, multicenter, international, open-label, multiple ascending-dose study to evaluate the safety and pharmacokinetics of tadalafil administered orally as a tablet or suspension to children with pulmonary artery hypertension (PAH). Spanning the target patient profile of ≥6 months to <18 years of age utilizing oral tadalafil doses selected to mimic typical drug exposures observed in adults with PAH with an open label long term extension.

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Protocol H6D-MC-LVIG
Phase 1b/2

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3. Revision History

SAP Version 1 was approved on 14 December 2012 (prior to first patient visit).

SAP Amendment 1 (Version 2) was circulated for approval on 29 August2012.

LY450190

4. Study Objectives

4.1. Primary Objective (Period 1)

To characterize the pharmacokinetics (PK) of tadalafil in a pediatric population with PAH and establish an appropriate dose range for further clinical research.

4.2. Secondary Objectives (Period 1)

- To assess the tolerability and safety of tadalafil in a pediatric population with PAH.

- To compare tadalafil PK profile in a pediatric population with historical adult data from Study LVGY.

- To determine appropriate dose ranges for use in the evaluation of efficacy and safety of tadalafil.

- To assess the palatability of the tadalafil suspension.

4.3. Open-label Extension Objectives (Period 2)

- To evaluate long-term safety while providing continued access to tadalafil for pediatric patients completing Period 1.

- To evaluate clinical worsening (CW), defined as any of the following: death, lung or heart transplantation, atrial septostomy or Potts shunt, hospitalization for PAH progression, new onset syncope, initiation of new PAH therapy, worsening of WHO functional class (see Protocol Attachment 4) by 1 or more (for patients unable to perform the six-minute walk test), or decreasing of 20% in the 6 minute walk (6MW) test distance (for those patients who are $\geq$ 6 years of age and able to perform the six-minute walk test and who have worsening of the WHO functional class).

- To evaluate the cardiopulmonary hemodynamic changes from baseline (Period1) to end of 3 month treatment in Period 2 as assessed by Echocardiography.

5. A Priori Statistical Methods

5.1 General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company or designee.

This study will contain two study periods: a PK/safety period (Period 1) and an open-label extension period (Period 2). Each patient will be permitted to continue in Period 2 for at least 2 years after participating in Period 1. Period 1 will consist of approximately 10 weeks of daily tadalafil administration, approximately 5 weeks (35 days) at each of two dose levels. In Period 2 pediatric patients who complete Period 1 will be given continued access to tadalafil for 2 or more years (or until the Sponsor concludes the study).

Patients will be recruited into 3 body-weight cohorts, namely:

Heavy: ≥40 kg

Middle: ≥25 kg to <40 kg

Light: <25 kg

The Heavy-weight and Middle-weight cohorts will be enrolled concurrently. Dosing and evaluation of the Middleweight cohort will be completed before enrolling patients in the Light-weight cohort.

It is planned that a minimum of 15 patients will complete the study (at least 5 in each body-weight cohort, of which ≥2 are not currently receiving endothelin receptor antagonist [ERA] PAH therapy and ≥3 are treated with ERA). A completer will be a patient who is assigned to treatment, receives approximately 5 weeks of low dose tadalafil and 5 weeks of high dose tadalafil, and completes a PK sample collection on putative steady state of high dose.

Summary tables will present separate results for each available weight cohort, as well as results across all qualifying patients. In each instance, if it is stated in this document that a summary by weight cohort will be presented it is implied that an overall summary across all cohorts will also be presented. Any additional or alternate ordering or grouping requirements for any individual table or listings will be specified in either this document or in the table or listing shells.

In listings where the patient is identified, data will be ordered by weight cohort, then by patient number; then by either assessment or start date, if applicable. Any additional or alternate ordering requirements for any individual listing will be specified in either in this document or the listing shells.

The WinNonLin computer program will be used to calculate the pharmacokinetic parameters; The SAS System will be used to perform all other statistical analyses.

Where appropriate, variables will be summarized descriptively (frequency and percent will be presented for categorical variables and for continuous variables the number of patients with non-missing observations, mean and standard deviation, as well as the median, minimum, and

maximum observed values). Any confidence intervals utilized will be two-sided, 95% confidence intervals.

Format requirements for specific output items will be noted in the specifications (programming requirements or shells) for the items.

All summaries and listings described in this document will be included in the CSR.

Additional exploratory analyses of the data will be conducted as deemed appropriate and will be described in the CSR as post hoc.

The baseline is Visit 2; if baseline data are missing, the last measurement taken prior to this visit will be used for the baseline measurement. Endpoint is the last non-missing measurement for the study period of interest.

When change from baseline is assessed or shift results are generated, only patients with a non-missing baseline and at least one non-missing postbaseline measurement will be included in the analyses. Only nonmissing continuous variable values will be reported under descriptive statistics.

5.2 Analysis Populations

Pharmacokinetic analyses will be conducted on the pharmacokinetic analysis population, which will include all data from all enrolled patients who receive at least one dose of tadalafil and have an evaluable PK profile. A PK profile will be considered evaluable if there are sufficient valid PK samples to permit the estimation of at least one key PK parameter (either C_{max} or AUC). Analyses will be according to the treatment the patient actually received.

Safety analyses will be conducted on the safety population, which will include all enrolled patients who took at least one dose of study medication, whether or not they completed all protocol requirements. Analyses will be according to the treatment the patient actually received.

The completer population is defined as all patients who are assigned to treatment and receive the 2 ascending dose levels of tadalafil administered once-daily and complete PK sample collection on putative steady- state of high dose.

There will be three cohorts defined according to the patient's weight at baseline. The heavy-weight cohort will consist of patients weighing 40 kg or more, the light-weight cohort will be those patients less than 25 kg and the middle-weight cohort will be patients in between ($\geq$25 kg to <40 kg).

No efficacy analyses are planned so no efficacy populations will be defined for this study.

5.3 Patient Disposition

All patients who discontinue from the study will be identified, and the extent of their participation in the study reported; if known, a reason for their discontinuation will be given. Patients who complete a study period will also be identified and their disposition reported for that study period.

Patient disposition will be summarized separately for each study period (Period 1 and Period 2) and for the overall study (both Period 1 and Period 2 together) using counts and percentages by weight cohort and overall; reason for discontinuation will be summarized for each visit by weight cohort and overall for the Safety population.

Patient disposition will be displayed graphically in a flowchart for all screened patients and listed for all patients in the Safety population. All available patient disposition information will be listed.

Patient allocation by investigator will be listed for all screened patients.

5.4   Treatment Compliance

Compliance with the study drug administration schedule will be assessed by summarizing the mean amount of study drug used per day compared with the expected amount of study drug to be taken daily. Study drug amounts will be determined from pill counts (for study drug administered as tablets) or changes in the weights of study medication bottles (for study drug administered as a suspension) that are collected on the eCRF at each study visit.

Compliance is defined as the ratio of the amount of study drug taken to the amount of study drug expected to be taken during a given time interval. The expected drug amount for the overall compliance calculation will be based on the number of days between the first dose of study drug and the last dose of study drug plus one day. Compliance will be summarized by weight cohort and overall as a continuous variable using descriptive statistics for the Safety population. The number and proportion of patients who have compliance of < 80%, between 80% and 120% (inclusive), and > 120%, respectively, will also be summarized by weight cohort and overall.

If the amount of drug returned at the final visit is missing (both pill counts and bottle weight) the patient's overall compliance will be considered missing.

All compliance information, including the calculated compliance values, will be listed.

5.5   Protocol Violations

Important protocol violations are defined as deviations from the protocol that could reasonably have an impact on patient safety, data integrity, or conclusions drawn from the study. A list of criteria used to identify important protocol violations that will be summarized for this study will be finalized as part of the data review prior to final database lock and will be included in the final study report.

Major protocol violations will be summarized for the Safety population. The summary will present the number and percent of patients with at least one major protocol violation at any time during the study and patients with no major protocol violations; this summary will be presented by weight cohort and overall. An additional summary by dose level will also be generated.

Major protocol violations will be listed for the Safety population.

5.6 Baseline Characteristics and Demographics

The patient's sex, weight, height, and other demographic characteristics will be recorded on the eCRF and may be used in the pharmacokinetic, pharmacodynamic, and safety analyses as quantitative or classification variables. The patient's age will be based on the patient's age at the screening visit and will utilize the birth date from the eCRF.

Demographic and baseline characteristics will be summarized by weight cohort and overall for the Safety population. If all patients are not exposed to both doses, additional summaries by dose level will also be generated. Historical illnesses will be coded using the MedDRA Dictionary and will be summarized by weight cohort, system organ class, and preferred term for the Safety population. Continuous variables will be summarized using descriptive statistics and categorical variables will be summarized using counts and percentages; all summaries will be presented by weight cohort and overall. Missing categorical variable values will be reported as a count under the category "Missing"; percentages will only be reported for nonmissing values and only counts of nonmissing variable values will comprise the denominator for the percentage calculation.

Historical illnesses will be listed for patients in the Safety Population. All available baseline characteristics and demographic results will be listed.

5.7 Prior Therapies and Concomitant Medications

Previous and concomitant therapies will be coded using the World Health Organization Drug Dictionary (WHODrug). Previous therapies are those therapies that started and stopped prior to the first dose of study drug. Concomitant therapies are those therapies that started on or after the first dose of study drug or those therapies that started prior to the first dose of study drug and were ongoing when the first dose of study drug was given. Previous and concomitant therapies will be summarized by weight cohort, drug class, and therapy name for the Safety population. Summaries will consist of the number and percent of patients taking a drug from each drug class and therapy name.

The frequency and percent of each weight cohort using concomitant ERA (bosentan or ambrisentan) will be presented. Other prior PAH therapies and use of other concomitant medications will be summarized by dose level and weight cohort and will be provided in a listing.

If a date is missing or only part of a date is reported (e.g., January, 2010), the available information will be used, if possible, to establish when the medication started or stopped relative to the first dose of study drug and the last dose of study drug. When expanding the previous therapy and concomitant therapy records across visits, the following imputation methods will be used:

 For start date:

- If only the day component is missing, then use the first day of the month.

- If only the month component is missing or both the day and month components are missing then use January 1.

- If only the year component is missing then use the year part of the consent date.

For end date:

- If only the day component is missing then use the last day of the month.

- If only the month component is missing or both the day and month components are missing then use December 31.

- If the year component is missing then use the study end date year.

All available prior therapy and concomitant medications will be listed.

5.8   Exposure

Duration of study drug exposure (in days) is defined as the difference between the date of last dose of study drug and the date of first dose of study drug plus 1. The dates of first dose and last dose of study drug will be collected on the electronic case report form (eCRF). Exposure will be treated as a continuous variable using the raw results only and will be summarized by weight cohort and overall using descriptive statistics. If either the date of first study drug dose or last study drug dose is missing, then duration of exposure will be considered missing. Only the overall study results (Periods 1 and 2 together) will be summarized. All available exposure results will be listed.

5.9   Pharmacokinetic Analyses

5.9.1 Samples for Pharmacokinetic Measurements

Blood samples will be collected predose and 2, 4, 8, 12, and 24 hours postdose on Days 1, 14, and 49, and used to determine the plasma concentrations of tadalafil. One trough PK sample will also be collected at second echocardiography day (Visit 10) to evaluate the tadalafil exposure after three month treatment during Period 2.

Plasma concentrations of tadalafil will be measured using a validated liquid chromatography–tandem mass spectrometry (LC-MS/MS) method at a laboratory approved by the Sponsor.

5.9.2 Pharmacokinetic Analysis Dataset

The tadalafil concentration data sheet will contain, at least, the patient identifier, study day, nominal sampling time, and concentration values. Clinical data including at least patient identifier, body weight, actual dose amount, dosing time, and actual and nominal PK sampling times will be obtained from the eCRF. A PK analysis dataset will be created by merging the

concentration data with the clinical data (using patient identifier and nominal PK sampling time as merge key fields) following the format specified by Eli Lilly. PK parameters will be calculated from the PK analysis dataset. The creation of PK analysis dataset, PK parameter calculation and creation of PK tables, listings, and figures will be conducted by ICON Development Solutions, LLC. Each analysis will be conducted twice; once for rapid (interim) analysis and safety review of the data during the trial using nominal sampling times, and again following the final study database lock using actual sampling times. The PK analysis dataset for the interim analysis will contain concentration data and dose amount. Demographic data may be included if available at the time of the interim PK analysis.

5.9.3 Noncompartmental Pharmacokinetic Analysis

5.9.3.1 Pharmacokinetic Parameters

The rules specified in the following Eli Lilly standard operating procedures (SOP) will be followed when performing the PK analysis and upon, where appropriate, consultation with the Sponsor:

- CCI

Evaluation of individual profiles during the study will be based on PK parameter estimates calculated by standard noncompartmental methods of analysis. The purpose of these analyses will be to evaluate dose escalations in individual patients, and to evaluate (as data become available) the appropriateness of the starting doses listed in Protocol Table LVIG.9.1.

The pharmacokinetic parameters will be calculated using the WinNonlin (Professional Network Edition, Version 5.2 or higher, Pharsight Corp, Palo Alto, CA), using a standard non-compartmental analysis (NCA) method.

PK parameters to be estimated for Day 1 will include but may not be limited to the following:

Parameter	Description
C_{max}	Maximum observed plasma concentration
t_{max}	Time to maximum observed plasma concentration
$AUC(0-t_{last})$	Area under the concentration-time curve from time zero to last measurable concentration, calculated using a combination of the linear and logarithmic trapezoidal methods. The linear trapezoidal method will be used up to t_{max} and then the logarithmic trapezoidal method after t_{max} (log-linear trapezoidal rule).
AUC_τ	Area under the plasma concentration-time curve over the dosing interval τ (i.e., 24 hours), calculated by the log-linear trapezoidal rule. For cases where the 24-hr sample concentration is below the quantifiable limit, this parameter will be treated as missing.

PK parameters to be estimated for Day 14 and Day 49 will include but may not be limited to:

Parameter	Description
C_{max}	Maximum observed plasma concentration
t_{max}	Time to maximum observed plasma concentration
$AUC(0-t_{last})$	Area under the concentration-time curve from time zero to last measurable concentration, calculated by the log-linear trapezoidal rule.
AUC_τ	Area under the plasma concentration-time curve over the dosing interval τ (i.e., 24 hours), calculated by the log-linear trapezoidal rule. For cases where the 24-hr sample concentration is below the quantifiable limit, this parameter will be treated as missing.
CL/F	Apparent plasma clearance, calculated as $Dose/AUC_\tau$.
C_{min}	Minimum observed plasma concentration
C_{av}	Average drug concentration, calculated as AUC_τ/τ.
PTF	Peak-trough fluctuation, calculated as $(C_{max} - C_{min})/C_{av} \times 100\%$
R_{Cmax}	Accumulation ratio for C_{max} as ratio of Day 14 to Day 1 or Day 49 to Day 1, calculated as C_{max} on Day 14 or Day 49 divided by C_{max} on Day 1
R_{AUC}	Accumulation ratio of AUC_τ as ratio of Day 14 to Day 1 or Day 49 to Day 1, calculated as AUC_τ on Day 14 or Day 49 divided by AUC_τ on Day 1

Actual elapsed time relative to the start of dosing will be used for all parameter estimations. Any parameter value excluded from summary statistics will be noted in the footnote of the summary table.

5.9.3.2   Treatment of Outliers

The rules specified in the following Eli Lilly SOP will be followed for the treatment of outlier PK data and upon consultation, where appropriate, with the Sponsor:

- CCI

Individual plasma concentrations, if deemed to be anomalous, may be excluded from the analysis at the discretion of the pharmacokineticist following a review of available documentation (e.g., bioanalytical report, clinical report). Any such exclusion will be communicated to the sponsor and clearly listed in the study report along with justification for exclusion.

Entire plasma concentration-time profiles for a patient may be excluded following review of available documentation (e.g., bioanalytical report, clinical report) and communication with the sponsor. Any such exclusion will be communicated to the sponsor and clearly listed in the study report along with justification for exclusion.

5.9.3.3 Non-quantifiable Concentrations

The following conventions apply to the calculation of PK parameters. All plasma concentrations reported as No Result (NR) values will be treated as missing and will appear in the data set as ".". The below the quantifiable limit (BQL) values that occur prior to the first quantifiable level will be treated as zero. All other BQL values will be treated as missing and set to ".".

5.9.4 Population Pharmacokinetic (PopPK) Analysis

Analysis of pharmacokinetic data for the purpose of characterizing tadalafil PK across the range of body weights and ages enrolled in the study and in each cohort; to evaluate the effect of various covariates such as age, body weight, sex, and ERA use on tadalafil exposure; and to predict appropriate dose(s) in subsequent pediatric studies of tadalafil will be the responsibility of the Sponsor and is beyond the scope of this document. The PopPK analysis methods will be described in a separate data analysis plan.

5.9.5 Descriptive Summaries of Pharmacokinetic Data

Formatting of tables, figures, listings, and abbreviations will follow the Eli Lilly Global PK/PD/TS Tool: NON-COMPARTMENTAL PHARMACOKINETIC STYLE GUIDE.

Plasma concentrations will be presented in descriptive summary tables, individual listings, mean profile plots, and individual profile plots. Summary statistics will be provided by weight cohort, ERA use, study day, dose, and nominal sampling time. Mean plasma concentration-time plots will display the arithmetic mean by cohort, dose, and nominal sampling time. If visual separation can be achieved, the standard deviation (SD) will also be displayed in these plots.

Descriptive summaries of plasma concentration will include N, arithmetic mean, SD, CV%, geometric mean, geometric CV%, median, minimum, and maximum values at each nominal sampling time.

The geometric mean will be calculated as the anti-log of the arithmetic mean calculated on log-transformed concentrations. The geometric CV% will be calculated using the variance calculated for log-transformed concentrations. Let s^2 represent the variance of log-transformed concentrations. The geometric CV% is estimated as $sqrt(exp(s^2-1)) \cdot 100\%$.

For descriptive summaries of plasma concentrations, BQL will be set to missing. Descriptive summary will be reported if the actual sampling time is within the below time window relative to the nominal collection time: $\pm20\%$ of 2 hours, $\pm15\%$ of 4 hours, $\pm10\%$ of 8 hours, ±1 hour of 12 hours, and ±2 hours of 24 hours. If less than 2/3 of the individual data points at a time point are quantifiable, descriptive summary may be reported if deemed appropriate, this must be flagged in the summary tables and noted in the study report.

For mean plasma concentration-time plots, pre-dose mean concentration on Day 1 will be set to zero. Otherwise, only quantifiable concentrations will be used to calculate mean concentrations. A mean concentration will be plotted if the actual sampling time is within the below time window relative to the nominal collection time: ±20% of 2 hours, ±15% of 4 hours, ±10% of 8 hours, ±1 hour of 12 hours, and ±2 hours of 24 hours. A mean concentration calculated with less than 2/3 concentrations may be included in the mean concentration-time plot, if deemed appropriate; this must be flagged in the mean plots and noted in the study report. If n = 1, the mean concentration will not be plotted. If n = 2, the mean concentration may be plotted if deemed appropriate.

Plasma PK parameters will be presented in descriptive summary tables and in data listings. Descriptive summaries of PK parameters will include N, arithmetic mean, SD, CV%, geometric mean, geometric CV%, median, minimum and maximum values. The t_{max} parameter will be summarized only with N, median, minimum, and maximum. The $t_{1/2}$ parameter will be summarized only with N, geometric mean, geometric CV%, median, minimum and maximum values.

5.10 Safety Analyses

5.10.1 Statistical Evaluation of Safety

Safety will be evaluated at each study visit by monitoring treatment-emergent adverse events, SAEs, and reasons for discontinuation. Body weight, height, clinical laboratory data (including NT-Pro-BNP results), cognitive functioning, physical examination results, vital signs, WHO-Functional Class, Tanner score, six-minute walk test, and ECG will also be used to evaluate safety.

Safety parameters will be listed and summarized overall and by weight cohort. Additional summaries by dose level will also be generated. Listings of safety data will also include the patient's concomitant ERA use (bosentan or ambrisentan (yes or no). Safety parameters to be assessed include spontaneously reported adverse events, clinical laboratory data, vital signs, physical examinations, and centralized 12-lead electrocardiograms (ECGs).

An overall summary of serious adverse events including deaths and discontinuations due to adverse events will be summarized by weight cohort with counts of the number of patients and percentages. A summary of all treatment emergent adverse events (TEAE) will be presented by system organ class and preferred term; there will be a similar presentation for TEAEs by relationship to study medication.

Continuous laboratory data will be summarized by weight cohort and visit with additional summaries by dose level also being generated.

Change from baseline to endpoint as measured by the WHO functional classification and six minute walk test (for patients ≥6 years of age); and percent increase in NT-Pro-BNP concentrations will also be summarized.

5.10.2   Adverse Events

An AE is any untoward medical event associated with the use of a drug in humans, whether or not it is considered related to a drug.

A TEAE is defined as an AE that first occurs or worsens (increases in severity) after first dose of study medication. An event that was ongoing prior to the first dose of study medication becomes treatment emergent if it worsens in severity after the first dose of study medication, as compared with the maximum severity prior to the first dose of study medication. For each event, the maximum severity prior to the first dose of study medication will be used as the baseline severity. If the maximum severity during postbaseline study visits is greater than the baseline severity, the event is considered to be treatment-emergent.

Adverse events (AEs) will be classified according to the Medical Dictionary for Drug Regulatory Affairs (MedDRA) and will be summarized as treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), discontinuations from treatment due to adverse events, adverse events reported as being possibly related to study drug, and AEs reported as possibly related to a study procedure. The subject incidence of adverse events will be summarized in the safety population by weight cohort and dose level. For summaries by MedDRA system organ class (SOC) and/or preferred term (PT), patients reporting 2 or more AEs with the same preferred term will be counted only once for that term using the highest reported severity. Patients reporting 2 or more AEs with different PTs that are in the same SOC will be counted only once in the SOC using the most severe event. For summaries by MedDRA system organ class (SOC) and/or preferred term (PT), patients reporting 2 or more AEs with the same preferred term, one of which is possibly related to study drug and one of which is not, the event will be counted only once using the possibly related to study drug event. Patients reporting 2 or more AEs with different PTs that are in the same SOC will be counted only once in the SOC; if any of the AEs are reported as being related to study drug then the event in SOC will also reported as being related to study drug. Summaries will consist of the number and percent of patients reporting an adverse from each system organ class and preferred term.

Every effort will be made to collect complete adverse event start dates, but if, despite all efforts, an adverse event start date is missing or partially missing (e.g., January, 2010), the following imputation method will be used:

- If only the day component is missing, then use the first day of the month.

- If only the month component is missing or both the day and month components are missing then use January 1.

- If only the year component is missing then use the year part of the consent date.

. The following adverse event displays will be presented:

- Overview of AEs

- TEAEs by SOC, preferred term PT, and weight cohort

- TEAEs by SOC, preferred term PT, and dose level

- AEs possibly related to study drug by SOC, preferred term PT, and weight cohort

- AEs possibly related to study drug by SOC, preferred term PT, and dose level

- AEs possibly related to study procedure by SOC, preferred term PT, and weight cohort

- AEs possibly related to study procedure by SOC, preferred term PT, and dose level

- Severity of TEAEs by SOC, preferred term PT, and weight cohort

- Severity of TEAEs by SOC, preferred term PT, and dose level

- Serious Adverse Events by SOC, preferred term PT, and weight cohort

- Serious Adverse Events by SOC, preferred term PT, and dose level

- AEs leading to discontinuation by SOC, preferred term and weight cohort

- AEs leading to discontinuation by SOC, preferred term and dose level

The overview of AEs will present summaries of overall AEs, overall TEAEs, serious AEs, deaths, AEs leading to discontinuation, AEs possibly related to study drug or study procedure, and severity of TEAEs.

The display of the intensity of TEAEs will summarize the severity levels for each TEAE by SOC, preferred term PT. For each TEAE, the severity level is recorded according to the patient's or physician's perceived maximum severity of the event (mild, moderate, or severe).

Tables presented by SOC and PT will be sorted in alphabetical order of SOC and by decreasing frequency of preferred term.

Weight cohort group summaries for TEAEs and SAEs will be summarized at the SOC and PT levels as will intensity of TEAEs.

A listing of all available pre-existing conditions and adverse events will be provided with treatment-emergent events indicated. Serious AEs, deaths, and AEs leading to discontinuation will be listed separately for patients in the Safety Population.

5.10.3   Clinical Laboratory Results

Raw and change from baseline values for all scheduled laboratory measurements (chemistry, urinalysis, and hematology analytes) will be summarized by visit and weight cohort; scheduled laboratory measurements are those designated in Appendix 2 of the protocol. Additional summaries by dose level will also be generated. All laboratory results will be appear in a clinical laboratory listing. For selected analytes that are reported as categories or intervals, summarization by counts and percentages will also be performed.

For each of the scheduled laboratory tests, a change from baseline to endpoint (LOCF) value will be summarized. The incidence rates of patients who have abnormally low or abnormally high laboratory values at any postbaseline visit will be provided by visit and weight cohort, with additional summaries by dose level also being generated.

Shifts in laboratory test values will be presented in terms of percent of patients with low, normal, and high, with respect to the normal range from baseline to each postbaseline time point. Covance reference ranges will be used for this study. Summary statistics for shift tables will be based on raw data.

Laboratory results that are reported as a one-sided interval will be analyzed at the endpoint value. For example, <20 will be analyzed as though it were reported as"20", however, "<20"will appear whenever such a value is listed.

Summary of laboratory test results (including shift tables) will be performed using SI units unless the results for a particular test are only provided using conventional units; in such a case conventional units will be summarized. Laboratory test results related to liver function (ALT, AST and total bilirubin) will also be classified using Covance conventional ranges and summarized by weight cohort in a table that presents counts and percentages of patients who met the following conditions at any postbaseline visit but not at baseline in each treatment period:

- ALT ≥ 3 upper limit of normal (ULN);

- AST ≥ 3 ULN;

- Total bilirubin ≥ 1.5 ULN

- ALT ≥ 3 ULN and total bilirubin ≥ 1.5 ULN; and

- AST ≥ 3 ULN and total bilirubin ≥ 1.5 ULN.

Abnormal laboratory values will be listed for all patients in the Safety Population. All available laboratory results will be listed.

Additional summaries specific to Inhibin B monitoring in male patients and NT-Pro-BNP results will also be generated; see Sections 5.10.8 and 5.10.14, respectively.

5.10.4 Physical Examination

Physical examinations and routine medical assessments will be conducted as specified in the protocol and as clinically indicated. Physical examinations will include an eye examination and Tanner Stage criteria and the eCRF will include these two assessments.

5.10.4.1 Eye Examination

Eye examinations will be performed at baseline, at the end of Period 1 and at the Year 2 visit in Period 2. The results for the measure will be treated as a categorical variable (normal, abnormal and not clinically significant, abnormal and clinically significant, and not done) and will be presented as counts and percentages. Shift results will also be presented as counts using a) normal, b) abnormal and not clinically significant, or c) abnormal and clinically significant as categories; any other categories will be treated as "missing" in the shift summaries. All summaries will be reported for each scheduled visit by weight cohort and overall. Additional summaries by dose level will also be generated.

Missing categorical variable values will be reported as a count under the category "Missing"; percentages will be reported under a separate "Missing" category for nonmissing values and these counts will be included in the denominator for the percentage calculation. All available eye examination results will be listed.

5.10.4.2   Tanner Stage

Tanner Stage criteria will be performed at the beginning of Period 1 and at the Year 1 and Year 2 visits in Period 2. If a patient has Tanner Score 5 on all criteria at a given visit, the subsequent Tanner Score evaluation will not be required.

The results for this measure will be treated as ordinal, categorical variables and will be presented as counts and percentages for each visit, as well as shift results; these will be presented by weight cohort and overall. Additional summaries by dose level will also be generated. Counts and percentages of patients that have progressed at least 1 Tanner stage will also be presented by visit.

The denominator for the counts of patients who progressed by at least one Tanner stage at a given visit will be based on those patients with both a nonmissing baseline and nonmissing value at that visit.

All available Tanner Stage results will be listed.

5.10.5   Vital Signs

Heart rate and blood pressure observations will be taken after the patient has lain in supine position for at least 2 minutes and will be recorded on the eCRF. Vital signs (heart rate, systolic blood pressure, and diastolic blood pressure) will be recorded at baseline, on Day 1, prior to first dose of study medication, and the end of Period 1 (i.e., at Week 10 or the final visit of Period 1), as well as Weeks 2, 5, and 7 during Period 1 and every three months during Period 2. When a new dose regimen is started (at Day 1 and at Week 5) heart rate and blood pressure observations will be taken at 30 and 60 minutes post dose and at 2, 3, 4, 5, and 6 hours post dose.

The vital sign results will be treated as a continuous variable using the raw results and change from baseline and will be summarized using descriptive statistics at each visit by weight cohort and overall. Additional summaries by dose level will also be generated. The multiple observations at Day 1 and Week 5 will be summarized separately, as though each time point were a separate visit. All available vital sign results will be listed.

Patient-specific plots of the multiple heart rate and blood pressure measurements over time will also be presented. Separate displays will be performed for Day 1 measurements and for Week 5 measurements; only nonmissing values will be plotted.

5.10.6   Weight and Height

Height and weight will be collected at baseline and endpoint of Period 1 and Years 1 and 2 in Period 2. Each variable will be treated as a continuous variable using the raw results and change from baseline and will be summarized using descriptive statistics at each visit by weight cohort

and overall. Additional summaries by dose level will also be generated. Only nonmissing continuous variable values will be summarized using descriptive statistics.

5.10.7   Electrocardiograms

Twelve-lead ECGs will be obtained according to the Study Schedule (Attachment 1). The ECGs will subsequently be electronically transmitted to the centralized ECG vendor designated by Lilly for storage. Any clinically significant findings that result in a diagnosis will be recorded by the investigator on the adverse event case report form (CRF) and will be analyzed and reported with adverse event data.

Abnormal ECG findings will be listed for patients in the Safety Population.

5.10.8   Inhibin Monitoring

Inhibin B monitoring will be performed for male patients at the beginning of Period 1 and at the Year 1 and Year 2 visits in Period 2. In patients below the age of 9 years, this will be an exploratory assessment. The results for the measure will be treated as a continuous variable using the raw results and change from baseline and will be summarized using descriptive statistics at each visit by weight cohort and overall. Additional summaries by dose level will also be generated. An additional summary will show separate results for patients below the age of 9 years as well as for patients aged 9 and above.

All available Inhibin B monitoring results will be listed in the laboratory data listings.

5.10.9   Cognitive Functioning

Cognitive functioning regarding verbal comprehension, perceptual reasoning, working memory, and process speed will be assessed using three scales, WISC-III and IV (Wechsler Intelligence Scale in Children), WAIS-III and IV (Wechsler Adult Intelligence Scale), and WPPSI-III (Wechsler Preschool and Primary Scale of Intelligence). These will be collected on the CRF at the beginning of Period 1 and at the Year 1 and Year 2 visits in Period 2.

The results for these measures will be treated as continuous variables and will be presented separately at each visit as a summary of the raw results and change from baseline by weight cohort and overall. Raw values and mean change from baseline to each postbaseline visit for continuous variables from all the above scales will be summarized at each visit and overall. An overall score for each subject visit (across test items) will not be generated.

All available cognitive functioning results will be listed.

5.10.10   WHO-Functional Class

WHO-functional class test results will be collected on the eCRF at baseline, the end of Period 1, and at each trimestral visit during Period 2. The results for this measure will be treated as an ordinal, categorical variables and will be presented as a summary of the raw results, change from baseline, counts and percentages, and shift results (i.e. improved, worsened or no change); these

will be presented by weight cohort and overall. Additional summaries by dose level will also be generated for Period 1.

Missing categorical variable values will be reported as a count under the category "Missing"; percentages will only be reported for nonmissing values and only counts of nonmissing variable values will comprise the denominator for the percentage calculation.

All available WHO-Functional Class results will be listed.

5.10.11   Six-Minute Walk (6MW)

The 6MW test will be measured in patients who are ≥6 years of age and who are developmentally able (mentally and physically) in the opinion of the investigator. An un-encouraged 6MW test assessment will be conducted at time points specified in the Study Schedule. The 6MW test will be recorded and evaluated by following 6MW test guidelines (see Protocol Attachment 6).

Six-minute walk test results will be collected on the eCRF at baseline and endpoint of Period 1 and at the Year 1 and Year 2 visits in Period 2. The results for the measure will be treated as a continuous variable using the raw results and change from baseline and will be summarized using descriptive statistics at each visit by weight cohort and overall. Similar summaries by dose level will also be generated for Period 1.

All available six-minute walk results will be listed.

5.10.12   Clinical Worsening (CW)

Clinical worsening will be evaluated during the study. Assessment of clinical worsening is defined as:

1. All cause mortality.

2. Lung or Heart-Lung Transplantation.

3. Atrial Septostomy or Potts Shunt.

4. Hospitalization for PAH progression:

> Hospitalization for PAH progression should not be due to a potentially precipitating event such as pneumonial hemoptysis etc.; however, if after the hospitalization is completed, the patient is discharged and the patient remains worse, then the patient can be assessed for clinical worsening.

5. Worsening of PAH

> Patient has any of the following criteria:
>
> > a. New onset syncope.

      b. Addition of new PAH specific concomitant therapy including but not restricted to epoprostenol or treprostinil, sildenafil, vardenafil, or increase in dose of existing PAH specific concomitant therapy (for example, ERA or beraprost).

      c. Increase of 1 or more in WHO Functional Class (Attachment 4) (except for patients already in Class IV) only for patients unable to perform the 6MW test.

      d) Decrease of 20% in 6MW tests (confirmed 5 to 10 days later) for children ≥ 6 years of age who are developmentally able to perform a 6MW test AND worsening WHO functional class.

Clinical worsening results will be taken from the Designated Adverse Event eCRF form, which is collected throughout the study. Once established, this measure will be treated as a binary, categorical variable and will be presented as counts and percentages of patients exhibiting clinical worsening. The individual items that form the basis for the clinical worsening determination will be presented in like manner, except that only affirmative reports will appear on the eCRF; for the individual items, missing will be considered to be equivalent to a negative response. Clinical worsening results and its components will be presented by weight cohort and overall. Additional summaries by dose level will be generated for Period 1. Time from the start of study drug to the first onset of clinical worsening will also be summarized using Kaplan-Meier estimation methods.

Missing categorical variable values will be reported as a count under the category "Missing"; percentages will only be reported for nonmissing values and only counts of nonmissing variable values will comprise the denominator for the percentage calculation.

All available clinical worsening determinations will be listed.

5.10.13   Palatability Questionnaire

Palatability questionnaire data (bitterness, sweetness, aftertaste, and overall) will be collected on the eCRF at the beginning and the end of Period 1. The results for this measure will be treated as ordinal, categorical variables and each variable will be presented descriptively using counts and percentages of each response, and as shift results; these will be presented by weight cohort and overall. Additional summaries by dose level will also be generated.

Palatability questionnaire results will be summarized as exploratory analyses. Details of the summaries are given in Section 5.10.

All available palatability questionnaire results will be listed

5.10.14   NT-Pro-BNP Results

N-terminal prohormone brain natriuretic peptide (NT-Pro-BNP) results will be obtained from patients at the beginning and end of Period 1. The results for the measure will be treated as a continuous variable using the raw results, change from baseline, and percent change from baseline and will be summarized using descriptive statistics at each visit by weight cohort and overall. Additional summaries by dose level will also be generated.

NT-Pro-BNP results will be summarized as exploratory analyses.

5.10.15 Echocardiograms

Echocardiogram results will be collected at baseline and endpoint (defined as the end of the first 3 months of treatment in Period 2). The variables (tricuspid annular plane systolic excursion, eccentricity index, pericardial effusion, maximal tricuspid regurgitant velocity) will be treated as continuous variables and will be summarized using descriptive statistics on raw values and change from baseline.

The results will be presented for each visit by weight cohort and overall. Additional summaries by dose level will also be generated. All available echocardiogram results will be listed.

5.11 Interim Analyses

Periodic interim analyses are planned for this study.

Two interim PK analyses will be conducted for each individual. The Day 1 and Day 14 PK data for the low dose will be analyzed together prior to proceeding to the high dose, and the Day 49 PK data for high dose will be analyzed subsequently. Pharmacokinetic parameters will be calculated as described in Section 5.9.2, with the exception that nominal sampling time will be used instead of actual sampling time. The input and output files for noncompartmental PK analysis will be provided to the sponsor in a format specified by the sponsor. Following the first interim PK analysis, data for all subsequent interim analyses will be added on to the same input file and appropriately versioned for subsequent interim analyses. The input file will include some demographic and lab data as specified by the sponsor.

When 5 patients from the Middle-weight cohort have completed Period 1, the safety, tolerability and summary of PK analyses from all patients will be reviewed by a safety monitoring committee (SMC). Based on this review, the SMC will advise Lilly as to the appropriateness of continuing the study and enrolling patients into the Light-weight cohort. Additional interim analyses for review by the SMC are planned at the completion of each cohort. The SMC will provide recommendations immediately after review. If necessary, additional SMC reviews will be performed prior to the lapsing of a full year since the previous SMC meeting. If an additional unplanned interim analysis is deemed necessary, the Lilly clinical research scientist or CRP/investigator will consult with the appropriate medical director or designee to determine if it is necessary to amend the protocol.

5.12 Safety Monitoring Committee

Output will be generated by a Statistical Analysis Center (SAC) that is independent of the study team in support of the independent Safety Monitoring Committee for this protocol. The responsibilities for this committee and the SAC supporting this committee are defined in a separate document, the Safety Monitoring Committee Charter.

A subset of the output items (tables, figures, listings) will be selected from those items designed for the final analysis. A minimum set will include:

- patient disposition and discontinuations

- demographics and patient characteristics

- patient disposition

- baseline disease characteristics

- study treatment changes

- prior and concomitant therapies

- preexisting conditions

- adverse events (including listings of SAE)

- deaths

- lab results

- eye examination

- six-minute walk test

- ECG abnormalities (as reported on adverse event pages)

- vital signs

- WHO functional class

- all available PK results.

5.13 Annual Report Analyses

While the study is ongoing, the following tables will be created using blinded data for each annual report. The annual report cutoff date will be established based on regulatory considerations. Standard baseline characteristics of age, gender, and origin will be summarized using descriptive statistics for all enrolled patients. TEAEs will be summarized sorted by decreasing frequency of Preferred Term within decreasing frequency of System Organ Class for those TEAEs occurring in $\geq 1\%$ of all treated patients. Adverse events reported as reason for discontinuation from the study (including any deaths) will be listed by patient for all enrolled patients.

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